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Search History

DATE: Monday, May 14, 2007 **Purge Queries** Printable Copy Create Case

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L5	L3 and (concentric)	11	L5
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L3	L2 and (vaccine or antigen)	116	L3
L2	multilamellar same (liquid adj2 crystalline)	190	L2
L1	multilamellar same (liquid adj2 crystalline) same (vaccine or antigen)	1	L1

END OF SEARCH HISTORY

L4: Entry 9 of 21 File: USPT Sep 4, 2001

DOCUMENT-IDENTIFIER: US 6284267 B1
** See image for Certificate of Correction **
TITLE: Amphiphilic materials and liposome formulations thereof

Brief Summary Text (6):
Liposomes are spherical vesicles of self-closed hydrated bilayers of amphiphilic lipids surrounding a generally central inner aqueous phase core which can differ in composition from the extraliposomal aqueous medium (Bangham and Horne, 1964). The lipid chains may be liquid-crystalline or solid-like gel phases. Liposomes are colloidal particles ranging in diameter from 20 nm to 5000 nm. Depending on the size and the number of constituent lamellar layers, these are classified as small or large unilamellar vesicles, and as multilamellar vesicles. The multilamellar vesicles have additional water layers trapped adjacent to the hydrophilic ends (polar head groups) between the regular dual arrays of the lipophilic (hydrophobic) alkyl chains (fatty tails).

Brief Summary Text (24):
The unique interfacial topography makes these novel amphiphilic materials and the derived self-assembled aggregates particularly appropriate for application in liposomal and micellar preparations suitable for passive and targeted drug delivery and antigen-presentation for diagnostics. The unique topography may be engendered additionally by equilibrating the hydrated novel amphiphiles with preformed liposomes and biological cells to create non-immunogenic red blood cells for blood substitutes and analogous biomaterials.

Brief Summary Text (57):
In further embodiments, the hydrophilic compound may further comprise a selected agent attached at a site distinct from said at least two hydrophobic moieties. Exemplary agents that may be attached in this manner are antibodies and antigens against which one desires to raise a humoral or cellular immune response. Other appropriate molecules are ligands for biological receptors, or in reciprocal embodiments, one or more biological receptor molecules.

Brief Summary Text (63):
Again, the resultant liposome may be advantageously combined with other surface-available components, such that the liposome comprises at least one surface-available antibody, antigen or binding ligand dispersed in the liposome bilayer or tethered to a component of the liposome bilayer.

Brief Summary Text (66):
The liposomes of the invention may be formulated with any one or more of the lipid components known to those of ordinary skill in the art. By way of example only, one may mention phospholipids, such as phosphatidylcholine; sterols, such as cholesterol, sphingolipids, such as sphingomyelin; and other components such as sucrose. By means of an exemplary embodiment only, the amphiphile-containing liposomes of the invention may contain the following constituents: between about 40 mole % and about 60 mole % amphiphile; between about 20 mole % and about 30 mole % of phosphatidylcholine; between about 5 mole % and about 10 mole % of sphingomyelin; with the optional addition of other components such as gangliosides and sucrose. Again, the liposomes may comprise in their outer bilayer one or more

surface-available components such as antibodies, antigens, binding ligands, receptors, or functional portions thereof. These components may be dispersed within the bilayer or covalently attached to a component thereof.

Brief Summary Text (68):
The type of selected agent that may be functionally associated with the liposomes of the invention is virtually limitless and those of skill in the art are referred to exemplary Tables 3A, 3B and 4. By way of example only, one may mention selected pharmacological agents, such as chemotherapeutic agents or cytotoxins (Table 3B); agents to combat infectious organisms, such as antibiotics, anti-virals and fungicides, particularly amphotericin B; immunological components, such as antibodies or fragments thereof, antigens, cytokines and anti-inflammatory agents in general; enzymes, hormones and neurotransmitters, anesthetics; blood components such as hemoglobin and coagulants; and a variety of nucleic acid molecules, constructs or vectors, including those that express any of the foregoing components and those that include antisense nucleic acids and ribozymes.

Drawing Description Text (9):
FIG. 7. Illustrative Biopodal Amphiphile Structures. Y=O, S, SS, NH, .dbd.N, HN (C .dbd.O), N-Alkyl, N,N-Dialkyl, N,N,N-Trialkylammonium, O(C.dbd.O), O(C.dbd.O)N, OP(.dbd.O)O.sub.2, and equivalent bond types. X=Reactive residue or linker for conjugation to antigens, antibodies, biotin, chelators, receptor-mimics, and analogues.

Drawing Description Text (10):
FIG. 8. Illustrative Tripodal Amphiphile Structures. X=Reactive residue or linker for conjugation to antigens, antibodies, biotin, chelators, receptor-mimics, and analogues.

Detailed Description Text (6):
The novel structural class of amphiphiles of the claimed invention represents a radical departure from existing structural motifs. Additionally, this molecular design engenders enhanced bilayer stability and unique topography of the liposomal surface barrier. Together, these attributes will result in increases, and even dramatic increases, in liposome blood circulation half-life. The novel amphiphiles may also be employed as functional components of other types of drug delivery vehicles. In fact, the unique structural and physicochemical properties of the disclosed amphiphiles render them useful in various biomedical applications and for use as blood substitutes, parenteral nutritional fat emulsions, antigen-presenting vehicles in diagnostics, and in skin and other personal care consumer products.

Detailed Description Text (12):
Several illustrative structures are shown in FIG. 7 and FIG. 8. These incorporate glycerol or pentaerythritol residues either as polymer branching points for providing functional groups within the polymer residue, or for attaching multiple lipid residues. Branching or multiple functional groups within the polymer may be provided by polyols and their block polymers, by hydroxy- and amino acids and peptides. The functional groups may be attached directly or via linkers/spacer residues to antigens, antibodies and other pendant ligands.

Detailed Description Text (23):
For certain applications, for instance in transfection and gene delivery vehicles, oligomeric or polymeric residues such as spermidine, spermine, polylysine, and related polyamine, polyethyleneamine, and polycationic materials are useful. Polypeptide residues are useful as mimics for cell membrane anchored receptors, and as antigens in diagnostics, and polyamino/cationic peptides for lung-surfactant replacement.

Detailed Description Text (37):
Hydrophilic polymers with more than two hydroxyl groups may be utilized for the

synthesis of the polypodal novel amphiphiles exactly as described for the bipodals. Synthesis as in EXAMPLE 1 through EXAMPLE 5 may be performed with an excess of the lipid to conjugate all hydroxyls, or alternatively, with a limited molar proportion of the lipid to generate a mixture of products with two or more lipid conjugands and one or more free hydroxyls. The latter are used as loci for attaching antigens, antibodies and like moieties, or additional pendant polymer residues, usually after replacement with more reactive residues such as thiol, or derivatization to an activated group, with or without a spacer or linker residue. The same type of chemistry is utilized also for linking the hydrophilic polymer to lipid moieties with intervening spacer residues.

Detailed Description Text (49):
The packing arrangements are dictated by the geometrical space requirements of the hydrated head groups and the fattyacyl hydrocarbon chains. The difattyacyl chain glycerophospholipids normally form lamellar bilayers. The crystal and the lyotropic phase structure and behavior of phospholipids, and methods for their study have been described in detail (Shipley, 1986; incorporated herein by reference). Lamellar bilayers above the hydrocarbon chain melting transition temperature (gel-to-liquid crystalline transition) on dilution with excess water and input of (mechanical) energy form the closed-end lamellar vesicles entrapping a part of the aqueous phase in the interior core forming liposomes. Liposomes may incorporate many bilayers (multilamellar; MLV)) or a single bilayer (unilamellar: ULV). The latter may be of small diameter and size (SUV) or relatively large (LUV) structures.

Detailed Description Text (58):
The novel structural class of amphiphiles of the claimed invention represents a radical departure from the existing structural motifs. Additionally, this molecular design engenders enhanced bilayer stability and unique topography of the liposomal surface barrier. Together, these attributes will result in increases, and even dramatic increase, in liposome blood circulation half-life. The novel amphiphiles may also be employed as functional components of other types of drug delivery vehicles. In fact, the unique structural and physicochemical properties of the disclosed amphiphiles render them useful in various biomedical applications and for use as blood substitutes, parenteral nutritional fat emulsions, antigen-presenting vehicles in diagnostics, and in skin and other personal care consumer products.

Detailed Description Text (60):
Micelles are formed on hydration of novel amphiphiles designed with branched hydrophobic moieties bearing multiple lipid chains. Microemulsions are produced by homogenization of triglyceride oil and novel amphiphile in aqueous buffer. The novel orientation and topography of multiple PEG chains in novel liposomes is appropriate also for micelles and microemulsions, and indeed any lipid-bearing hydrophobic surface. The latter include the lipid bilayer membranes of biological cells. Thus a new cell surface is generated on treatment with novel amphiphile and comprises a poly-anchored PEG/polymer coat eclipsing the surface antigens. On the other hand, the poly-anchored PEG/polymer coat around a synthetic lipid assembly is most appropriate for attaching antigenic ligands for use in diagnostic test kits, and for supporting antibodies for targeting therapeutic liposomes to desired tissue cells.

Detailed Description Text (63):
In conventional liposomes, whether multilamellar vesicles (MLV) or unilamellar vesicles (ULV), the hydrated lipid bilayers are present in the liquid-crystalline (L.sub..alpha.) or the gel (L.sub..beta., L.sub..beta..) phases at physiological temperature depending principally on the main chain melting transition (T.sub.c) of the component lipids. The effect of polypodal amphiphiles as additional lipid components on the gross morphology and phase structure may be visualized as follows. p As a first approximation, the lipid ends in bipodal PA-PEG-PA with infinitely long PEG chain length may be regarded as two independent anionic

phospholipids. This independence is indicated also by molecular models which suggest that long PEG chain permits a high level of flexibility and conformational mobility for the terminal lipid residues. Therefore, at low molar proportions, the anionic phospholipid residues of PA-PEG-PA will get incorporated into the bilayer as is observed with phosphatidylglycerol and analogous phosphatidyl-alkylester phospholipids. Such additives cause only a minimum of perturbation of the lyotropic phase of the lipid bilayer. Statistical mixing and the repulsive influence of the head group anionic charge promote wide separation between individuals. The morphology and effects of the PEG link between the terminal phospholipids spaced far apart in the lipid bilayer can then be considered.

Detailed Description Text (151):
The hydrates were equilibrated by vortex mixing, repeated cycles of freezing and thawing, and incubation above the T.sub.c. Some of these preparations were examined in a polarized light microscope and these showed birefringence (myelin figures) characteristic of multilamellar bilayer structures (MLVs). The MLVs were stored at ambient temperature for 24 h. The liquid crystalline phase status of these hydrates was characterized by X-ray diffraction as described in EXAMPLES 7, 8 and 9. Dilution with additional quantity of the aqueous phase followed by sonication in bath sonicator (Laboratory Supplies Co., Hicksville, N.Y.) and/or extrusion of the MLVs through 100 .mu.m pore diameter polycarbonate membranes (MacDonald et al., 1991) yielded ULVs. The ULVs were characterized and employed for encapsulation studies, e.g., of calcein as drug model in EXAMPLE 10.

Detailed Description Paragraph Table (5):
TABLE 4 Additional Selected Agents Oxygen Carriers Haemoglobin Perfluorinated Lipid novel amphiphiles Nutrient/Parenteral Fat emulsions Omega-3-glycerides Fat soluble vitamins Tocopherols Contrasting Agents Gadolinium complexes Barium meal Antigen presenting vehicles (Novel amphiphiles with attached ligands) Lectin RGD Immunogenic peptides Interleukins CSFs LFAs Interferons Immunoglobulins

Current US Original Classification (1):
424/450

CLAIMS:

46. The amphiphilic molecule of claim 43, wherein said liposome further comprises at least one surface available antibody, binding ligand or antigen disposed in the liposome bilayer or tethered to a component of the liposome bilayer.

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L5: Entry 5 of 11 File: USPT Mar 2, 2004

US-PAT-NO: 6699499
DOCUMENT-IDENTIFIER: US 6699499 B1
** See image for Certificate of Correction **

TITLE: Amphiphilic materials and liposome formulations thereof

DATE-ISSUED: March 2, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Aneja; Rajindra	Ithaca	NY		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Nutrimed Biotech	Ithaca	NY			02

APPL-NO: 09/879368 [PALM]
DATE FILED: June 11, 2001

PARENT-CASE:
The present application is a divisional application of U.S. application Ser. No. 08/912,978, filed Aug. 13, 1997, which claims priority to provisional application Ser. No. 60/024,382, filed Aug. 14, 1996, the entire text and figures of which disclosure are specifically incorporated herein by reference without disclaimer.

INT-CL-ISSUED: [07] A61K 9/127

INT-CL-CURRENT:

TYPE	IPC	DATE
CIPS	A61 K 8/14	20060101
CIPS	C07 F 9/00	20060101
CIPS	C07 F 9/10	20060101
CIPS	C08 G 65/00	20060101
CIPS	C08 G 65/329	20060101
CIPS	C08 G 65/335	20060101
CIPS	C08 G 65/337	20060101
CIPS	A61 K 8/72	20060101
CIPS	A61 K 9/127	20060101
CIPS	A61 K 8/86	20060101
CIPS	A61 Q 19/00	20060101
CIPS	C11 D 17/00	20060101

US-CL-ISSUED: 424/450; 424/1.21, 424/9.321, 424/9.51, 424/417, 424/94.3, 428/402.2, 554/79, 554/80, 554/103, 554/227

US-CL-CURRENT: 424/450; 424/1.21, 424/417, 424/9.321, 424/9.51, 424/94.3, 428/402.2, 554/103, 554/227, 554/79, 554/80

FIELD-OF-CLASSIFICATION-SEARCH: 424/450, 424/1.21, 424/9.321, 424/9.51, 424/417, 424/94.3, 428/402.2, 436/829, 554/76, 554/80, 554/103, 554/227
See application file for complete search history.

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

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	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	4772471	September 1988	Vanlerberghe et al.	424/450
☐	4830857	May 1989	Handjani et al.	424/450
☐	4837028	June 1989	Allen	424/450
☐	4920016	April 1990	Allen et al.	424/450
☐	5013556	May 1991	Woodle et al.	424/450
☐	5153000	October 1992	Chikawa et al.	424/450
☐	5225212	July 1993	Martin et al.	424/450
☐	5395619	March 1995	Zalipsky et al.	424/450
☐	6284267	September 2001	Aneja	

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	CLASS
0370491	April 1995	EP	

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ART-UNIT: 1615

PRIMARY-EXAMINER: Kishore; Gollamudi S.

ATTY-AGENT-FIRM: Williams, Morgan and Amerson

ABSTRACT:

Disclosed is a new structural class of amphiphilic molecules which incorporate a hydrophilic material or polymer attached, at spatially distinct sites, to at least two hydrophobic residues. Certain of the amphiphilic molecules comprise a plurality of hydrophobic moieties. All such amphiphilic molecules have a common structural motif and, in contact with water, display surface activity and self-assemble into multimolecular aggregates and liquid crystalline phases. Also disclosed are enhanced stability liposomes that incorporate such amphiphilic molecules via unique interactions, and methods of using such formulations in a variety of applications including drug delivery, nutrition, bio-diagnostics, cosmetics, blood products and related applications.

45 Claims, 10 Drawing figures

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L1: Entry 1 of 1 File: USPT Dec 5, 2000

DOCUMENT-IDENTIFIER: US 6156337 A
TITLE: Method for high loading of vesicles with biopolymeric substances

Drawing Description Text (43):
The selection of phospholipids for the lipsomal vaccine preparation is based on two main parameters: (i) chemical stability; (ii) uptake by macrophages. Surprisingly, the selection of dimyristoyl phosphatidylcholine (DMPC) and dimyristoyl phosphatidylglycerol (DMPG) as the raw material for liposome preparation was advantageous. These disaturated phospholipids are not susceptible to various oxidation processes. Their gel to liquid crystalline phase transition (T.sub.m) is 24.degree. C., and therefore at 37.degree. C. the lipids are in their liquid crystalline state, which is preferred for uptake by macrophages. The negative charge introduced by the DMPG also increases liposome uptake by macrophages which serve as antigene presenting cells. Large liposomes (multilamellar large vesicles) are advantagaeous due to their preferred uptake by the macrophages.

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